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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/820,215	03/27/2001	Scott A. Waldman	08321-0166 US	2195

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EXAMINER	
SPIEGLER, ALEXANDER H	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 02/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/820,215	WALDMAN ET AL.	
	Examiner	Art Unit	
	Alexander H. Spiegler	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-11,13-15 and 37-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-11,13-15 and 37-47* is/are rejected.

7)☒ Claim(s) *2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. This action is in response to Applicants' response, filed on November 10, 2003. Currently, claims 1-4, 6-11, 13-15 and 37-47 are pending and are rejected. This action is made NON-FINAL. Any objections and rejections not reiterated below are hereby withdrawn.

Specification

2. The disclosure is objected to because of the following informalities:

A) The use of the trademarks has been noted in this application. These trademarks should be capitalized wherever they appear and be accompanied by the generic terminology. (See, for example, pages 7, 16-17, 23, 27, 29, etc.).

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

B) Page 25, line 7, recites "- 4^0?", which appears to be a typographical error and could be amended to delete "?".

Appropriate correction is required.

Claim Objection

3. Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim (i.e., Claim 1). Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent

form, or rewrite the claim(s) in independent form. Claim 1 recites that the epithelial cell marker is a "differentiation-specific antigen" and Claim 2 recites that the epithelial cell marker is a tissue-specific marker. On page 12, the specification states, "tissue-specific marker (also called differentiation specific antigens", which therefore asserts that these words have the same meaning. Accordingly, because these words are synonyms, Claim 2 does not further limit Claim

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-4, 6-11, 13-15 and 37-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-4, 6-11, 13-15 and 37-47 are indefinite because Claim 1 is drawn to a method for detecting the presence of a disseminated epithelial cell marker, however, the final step is for detecting the presence of mRNA. The claims do not set forth the relationship between detecting the presence of mRNA and detecting the presence of a disseminated epithelial cell marker. Therefore, it is not clear as to whether the claims are intended to be limited to a method of detecting the presence of a disseminated epithelial cell marker or detecting the presence of mRNA.

B) Claims 1-4, 6-11, 13-15 and 37-47 over "disseminated epithelial cell marker" because it is not clear as to what is meant by this recitation. For example, it is not clear as to whether the marker is specific for epithelial cells from the outset, or the marker begins as a non-specific

epithelial cell marker, but later becomes specific for epithelial cells after dissemination. Furthermore, the specification does not specify which epithelial cell markers are considered to be "disseminated" or which epithelial cell markers are capable of being "disseminated".

New Matter

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 4 and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 4 has been amended to (and newly added Claim 40) recite, "the disseminated epithelial cell marker consisting of "guanylyl cyclase, Cdx-1...tyrosine hyroxylase, and neuron-specific glycoprotein". That is, Claim 4 has been amended (and Claim 40 newly added) to assert that all of the markers listed in these claims are "epithelial" cell markers. However, neither the specification nor the claims previously asserted that all of the markers in Claim 4 (or Claim 40) are considered to be "epithelial" cell markers. For example, on page 12, lines 10-27, the specification only refers to the markers listed in Claim 4 (and Claim 40) as "disseminated cell markers", but not specifically, that the markers are "epithelial" cell markers. Furthermore, on page 10, lines 7-10, the specification states, "epithelial cell-specific markers including GC-C,

prostate-specific antigen (PSA), prostate-specific membrane antigen (PSM), carcinoembryonic antigen (CEA), cytokeratin-19 (CK-19), cytokeratin-20 (CK-20), mucin 1 (MUC-1), and gastrointestinal-associated antigen (GA733.2)." Accordingly, while the specification provides support for the assertion that the markers listed on page 10, lines 7-10, are "epithelial" cell markers, the specification does not provide support for the newly amended Claim 4 (or newly added Claim 40), which assert that markers other than those listed on page 10, lines 7-10, are "epithelial" cell markers.

If Applicants' traverse this rejection, Applicants' should specifically point out (by page and line number), where there is support for newly amended Claim 4 (and newly added Claim 40).

Written Description

8. Claims 1-4, 6-11, 13-15 and 37-47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to methods of detecting the presence of *a disseminated epithelial cell marker* in a sample comprising the steps of

a) eliminating CD34+ cells from the sample; and

b) *detecting the presence of mRNA that encodes the marker, wherein the marker is a differentiation-specific antigen.*

(emphasis added).

Thus, the claims are drawn to methods of detecting "disseminated epithelial cell markers", wherein after the elimination of CD34+ cells, "mRNA that encodes the marker, wherein the marker is a differentiation-specific antigen" is detected. Accordingly, the claims are drawn to detecting the genus of "mRNA that encodes a disseminated epithelial marker, wherein the marker is differentiation specific".

This genus comprises the class of compounds (mRNAs) that share a function (encoding a disseminated epithelial cell marker, wherein the marker is a differentiation-specific antigen). However, the specification does not specify a common structure of this class of mRNAs. That is, while the members of the genus encompassed by the claims (e.g., the mRNA encoding a disseminated epithelial cell marker, wherein the marker is a differentiation-specific antigen), share a function, they do not share a structure that is similar. Each mRNA encompassed by the genus will have different structure, absent any disclosed structural similarities provided by the specification. That is, even assuming, the mRNAs encompassed by the genus are functionally similar, they are not structurally similar, and therefore, the functional description of the mRNAs does not provide adequate written description to the plurality of other structurally distinct mRNAs that are encompassed by the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession* of the invention. The invention is, for purposes of the written description inquiry, *whatever is now claimed* (See page 1117)." (emphasis added)

Additionally, in *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement, which defines a genus of nucleic acids by

only their functional activity, does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the specification teaches eight epithelial cell markers (see page 10, lines 7-10), and asserts these epithelial cell markers "can be" used as disseminated markers (see page 12, lines 10-27). However, these markers are not structurally related, nor do they share any common sequences, and therefore, these eight species are not considered to be a representative number of species. It is then determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g., similar structural motifs, sequence similarity, etc.). In the instant case, no such identifying characteristics have been provided for any of the claimed nucleic acids. Furthermore, it is noted that the specification does not describe which mRNA are specific for which "differentiation-specific antigen". In other words, the specification does not describe which mRNAs are specific for a particular tissue-specific marker.

Accordingly, because the specification does make clear that Applicants were in possession of the genus of mRNAs that encode disseminated epithelial cell markers, wherein the

cell markers are differentiation-specific antigens, at the time the application was filed, the claims lack adequate written description.

Applicant's attention is also drawn to the "Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, 1st Paragraph, Written Description Requirement" (published in Federal Register/Vol. 66, No. 4/Friday, January 5, 2001/Notices; p. 1099-1111).

Enablement

9. Claims 1-4, 6-11, 13-15 and 37-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting the presence of an epithelial cell marker in a sample containing CD34+ cells, comprising the steps of a) eliminating CD34+ cells from the sample; and b) detecting the presence of said epithelial cell marker, wherein said epithelial cell marker is selected from the group consisting of CEA, PSA, PSM, CK-19, CK-20, MUC-1 and GA733.2, does not reasonably provide enablement for methods of detecting the presence of a disseminated epithelial cell marker in a sample comprising the steps of a) eliminating CD34+ cells from the sample; and b) detecting the presence of mRNA that encodes the marker, wherein the marker is a differentiation-specific antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

MPEP 2164.01 states:

> Even though the statute does not use the term 'undue experimentation,' it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation.

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)

The *Wands* court outlined several factors to be considered in determining whether a disclosure would require undue experimentation. These factors include, but are not limited to:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Id. at 1404.

In the instant case, the specification does not enable one of skill in the art to make and use the claimed invention for the following reasons:

(1) ***Nature of the Invention & Breadth of the Claims***

The claims are drawn to methods of detecting the presence of *a disseminated epithelial cell marker* in a sample comprising the steps of

a) eliminating CD34+ cells from the sample; and

b) *detecting the presence of mRNA that encodes the marker, wherein the marker is a differentiation-specific antigen.*

(emphasis added).

Thus, the claims are drawn to methods of detection "disseminated epithelial cell markers", wherein after the elimination of CD34+ cells, "mRNA that encodes the marker, wherein the marker is a differentiation-specific antigen" is detected. Accordingly, the claims are drawn to detecting the genus of "mRNA that encodes a disseminated epithelial marker, wherein the marker is differentiation specific".

(2) ***Relative Skill of those in the Art, State of the Prior Art, Amount of Direction or Guidance Presented & Presence or Absence of Working Examples***

The specification teaches eight epithelial cell markers (see page 10, lines 7-10), and asserts these epithelial cell markers "can be" used as disseminated markers (see page 12, lines 10-27). Specifically, the specification teaches the removal of CD34+ cells from peripheral blood (or mononuclear cells) reduces illegitimately transcribed epithelial cell-specific transcripts of CEA, PSA, PSM, CK-19, CK-20, MUC-1 and GA733.2 (see examples 6-7 on page 30). That is, the specification teaches only the illegitimate transcription of eight specific epithelial cell markers (CEA, PSA, PSM, CK-19, CK-20, MUC-1 and GA733.2) that are found in specific types of samples (e.g., peripheral blood or mononuclear cells) can be reduced.

However, the specification does not provide any guidance on any other types of mRNA which encode disseminated epithelial cell markers (wherein said marker is a differentiation-specific marker) or samples comprising said cell markers, nor does the specification provide any guidance on the reduction of illegitimate transcription of any other disseminated epithelial cell markers. For example, the specification does not teach which mRNAs are specific for a particular differentiation-specific antigen. Furthermore, the specification does not specify which differentiation-specific antigen the eight epithelial cell markers are specific for.

Accordingly, the relative skill in the art is high.

(3) ***Quantity of Experimentation Necessary & the Unpredictability of the Art***

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. In *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of

ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art.

In order to carry out making and using of the mRNAs encompassed by the claimed invention, the experimentation required by the skilled artisan would be considered undue. First, the skilled artisan would have to experiment in order to make or use mRNAs that encode "disseminated epithelial cell markers, wherein the marker is a differentiation-specific antigen". This would encompass not only determining what mRNAs encode "disseminated epithelial cell markers", but what differentiation-specific antigens the mRNAs are specific for. No guidance is given in the specification for this type of experimentation. Even assuming to skilled artisan could experiment to determine the mRNAs encompassed by the claimed invention, the artisan would still have to experiment to determine what effects the elimination of CD34+ cells would have on detecting the presence of the mRNA, and whether this elimination step would reduce illegitimate transcription. Such experimentation requires a large amount of trial and error analysis, with little to no starting point, absent any teaching in the specification regarding any common structural features from the genus of mRNAs encompassed by the specification or how to determine what differentiation-specific antigen is specific for each mRNA of the genus (see above), wherein the results of such analysis are unpredictable, and is therefore considered undue.

In essence, the experimentation that one skilled in the art would be required to perform is in fact the proposed novelty of the invention. However, "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". (*Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001).

Accordingly, in view of the unpredictability in the art and in view of the lack of specific disclosure in the specification, undue experimentation would be required to practice the invention as it is claimed.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-4, 7-11 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Zippelius et al. (Journal of Clinical Oncology (1997) 15(7): 2701-2708, cited in the IDS).

Regarding, Claims 1-4 and 13, Zippelius teaches methods of detecting the presence of a disseminated epithelial cell marker (e.g., CEA, erb-B2, erb-B3, CK-18, PSM) in a sample comprising the steps of

a) eliminating CD34+ cells from the sample (e.g., removing a fraction of mononuclear cells (which comprise CD+34 cells) before RT-PCR, see page 2702, column 1, under section titled, "Patients and BM Preparation"); and

b) detecting the presence of mRNA that encodes the marker, wherein the marker is a differentiation-specific antigen (e.g., prostate or breast).

(see abstract and pages 2702-3).

It is noted that the removal of mononuclear cells before RT-PCR meets the limitation of "eliminating CD34+ cells", since mononuclear cells from bone marrow will contain CD34+

cells. Furthermore, the claims are drawn to "eliminating CD34+ cells", which can be interpreted as only eliminating a fraction of the mononuclear cells.

Regarding Claims 7-8, the sample was bone marrow (see abstract and page 2702).

Regarding Claims 9-11, mRNA is detected by a "nested" RT-PCR (see pages 2702-3).

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1-4, 7-11, 13, 37-40 and 42-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ts'o et al. (USPN 5,962,237), in view of Palsson, B. (USPN 5,874,266).

Ts'o teaches methods of isolating and enriching rare cells (i.e., tumor cells) from body fluids (e.g., blood), by negative selection of non-tumor cells such as white blood cells from the CD family (see abstract, col. 1, lines 8-13, and col. 5, lines 40-51, col. 10, line 5 to col. 12, line 35, see also generally, cols. 2-5 and 11-16).

Regarding, Claims 1-4, 13, 37-40 and 45, Ts'o teaches methods of detecting the presence of a disseminated epithelial cell marker (e.g., PSA and PSM) in a sample comprising the steps of

a) eliminating nucleated white blood cells (e.g., mononuclear cells and cells from the CD family) from the sample (col. 1, lines 8-13, and col. 5, lines 40-51, col. 10, line 5 to col. 12, line 35); and

b) detecting the presence of mRNA that encodes the marker, wherein the marker is a differentiation-specific antigen (e.g., prostate) (col. 14-16, for example).

Regarding Claims 7-8, the sample was blood (col. 5, lines 48-51, for example).

Regarding Claims 9-11 and 42-44, mRNA is detected by a "nested" RT-PCR (col. 16, lines 47-65, for example).

Ts'o also teaches,

> The rare cells enriched according to this embodiment are substantially free of contamination by non-rare cells. For example, *in the case of the separation of cancer cells from blood, it was found that the cancer cells could be almost completely separated from nucleated white blood cells. This can be advantageous because nucleated white blood cells, if present, can interfere with cell identification, particularly for some of the embodiments wherein polymerase chain reaction (PCR) methods are used.*

> For some of the embodiments wherein the fluid comprising rare cells and non-rare cells is blood, *it may be desirable to use antibodies that bind to white blood cells (leukocytes)* and/or red blood cells (erythrocytes). *Examples of suitable leukocyte antibodies include the human and anti-human leukocyte CD antibodies*, e.g., CD2, CD3, CD4, CD5, CD7, CD8, CD11a, CD11b, CD11c, CD14, CD15, CD16, CD19, CD20, CD28, CD36, CD42a, CD43, CD44, CD45, CD45R, CD45RA, CD45RB, CD45RO, CD57, and CD61 antibodies, *and the like*.

(emphasis added) (col. 11, line 53 to col. 12, line 4).

Accordingly, Ts'o teaches that it is advantageous to eliminate mononuclear white blood cells (e.g., cells from the CD family) from the cancer cells because these mononuclear white blood cells cause contamination (e.g., illegitimate transcription) during PCR assays and analysis. Ts'o teaches eliminating members of the CD cell family are desirable, but does not teach removing CD34+ cells.

However, Palsson teaches eliminating CD34+ cells from tumor cells is advantageous to ensure isolation of only the tumor cells (col. 2, lines 21-31). Palsson also teaches that this negative CD34+ selection can be used in conjunction with detection of epithelial cell markers (col. 2, lines 31-34).

Accordingly, in view of the teachings of Palsson, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Ts'o so as to have eliminated CD34+ cells from rare cancer cells. One of ordinary skill in the art would have been motivated to modify the method of Ts'o to have eliminated CD34+ cells, in order to have achieved the benefit of providing a more effective means of detecting epithelial cell markers by reducing contamination caused by the CD34+ cells.

16. Claims 6 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ts'o et al. (USPN 5,962,237), in view of Palsson, B. (USPN 5,874,266), as applied to Claims 1-4, 7-11, 13, 37-40 and 42-45 above, and in further view of

The teachings of Ts'o and Palsson are presented above. The references teach methods of detecting epithelial cell markers, comprising eliminating CD34+ cells, and detecting mRNA encoding said cell marker, wherein said cell marker is a differentiation-specific antigen. The references teach eliminating the CD34+ cells using anti-CD34 antibodies attached to immunoaffinity beads. The references do not specify that this method of using beads and anti-CD34 antibodies is a method of column chromatography.

However, Elliot teaches the elimination of CD34+ using a CD34 Progenitor Cell Isolation Kit (QBend/10) made by Miltenyi Biotech GmbH, wherein "cells are tagged with an anti CD34 monoclonal antibody they were then bound to magnetic microspheres according to protocol. The tagged cells were next passed through pre-filled MiniMacs separation columns, the columns were washed and the CD34+ cells were then eluted from the column." (col. 22, lines 34-41). Elliot teaches this column chromatography protocol results in higher purity isolation of the CD34+ cells.

Accordingly, in view of the teachings of Elliot, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Ts'o and Palsson so as to have used column chromatography for eliminating the CD34+ cells. One of ordinary skill in the art would have been motivated to modify the method of Ts'o and Palsson in order to have achieved the benefit of providing a more effective means of isolating and diluting out the CD34+ cells to ensure a better isolation and analysis of the rare tumor cells.

17. Claims 14-15 and 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ts'o et al. (USPN 5,962,237), in view of Palsson, B. (USPN 5,874,266), as applied to Claims 1-4, 7-11, 13, 37-40 and 42-45 above, and in further view of Waldman et al. (Cancer Epidemiology, Biomarkers & Prevention (1998) 1: 505-514, cited in the IDS).

The teachings of Ts'o and Palsson are presented above. The references teach methods of detecting epithelial cell markers, comprising eliminating CD34+ cells, and detecting mRNA encoding said cell marker, wherein said cell marker is a differentiation-specific antigen. The references teach the rare cells can be epithelial cells (i.e., comprising epithelial cell markers, such as PSA and PSM, see col. 13, lines 56-67, for example), but do not teach the method wherein the epithelial cell marker is GC-C.

However, Waldman teaches the detection of GC-C, which is an epithelial cell marker for colorectal cancer, and can be used in diagnosing colorectal cancer, one of the most common forms of cancer (see abstract, page 505, 1st column and pages 510 and 512).

Accordingly, in view of the teachings of Waldman, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Ts'o and Palsson so as to have detected the epithelial marker, GC-C. One of ordinary skill in the art would have been motivated to modify the method of Ts'o and Palsson in order to have achieved the benefit of providing a means of diagnosing colorectal cancer, which is one of the most common forms of cancer.

Conclusion

18. No claims are allowable.

19. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Wang et al. (US 2002/0098535), incorporating the teachings of Ts'o (see pages 2-8).

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (571) 272-0788. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner are unsuccessful, the primary examiner in charge of the prosecution of this case, Carla Myers, can be reached at (571) 272-0747. If attempts to reach Carla Myers are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (571) 272-0782. The fax number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Alexander H. Spiegler
February 6, 2004

CARLA J. MYERS
PRIMARY EXAMINER